EFFECTIVENESS OF 48 WEEKS INTERFERON ALFA 2-B IN COMBINATION WITH RIBAVIRIN AS INITIAL TREATMENT OF CHRONIC HEPATITIS

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Background: Chronic hepatitis C is a common problem worldwide and is becoming an increasingly common problem in Pakistan. This study was done to evaluate effectiveness and safety of 48 weeks combination treatment with Interferon and Ribavirin as initial therapy of chronic hepatitis C patients. **Methods:** One hundred consecutive patients were prospectively evaluated and treated with combination of Interferon Alfa 2-b three million units subcutaneously three injection weekly and Ribavirin 800-1200 mg orally daily for 48 weeks and followed for another 6 months. End of the treatment, sustained viral response and side effects were noted. **Results:** Of one hundred patients, 98 completed the treatment. There were 55 males and 43 females. Ages range from 21-60 years, mostly being 31-55 years. Over 83% responded at the end of treatment and four relapsed. Out of treated, 72.7% males and 88.3% females had sustained viral response with a total combined sustained viral response rate of 79.5%. Patients with cirrhosis had 85.7 sustained viral response. Four percent patients took longer than three months to show HCV RNA negativity. Side effects were usual and tolerable and only 2% discontinued the treatment. Non-responders were mostly males above age 50. **Conclusion:** Forty-eight weeks combination treatment with Interferon alfa 2-b and Ribavirin has given 79.5% sustained viral response in our patients and treatment was well tolerated.

Key Words: Chronic hepatitis C, Interferon, Ribavirin

INTRODUCTION

Chronic hepatitis C is a common problem worldwide[1,2] and is becoming an increasingly common problem in Pakistan[3-5] where the spread of the hepatitis C has been due to unsafe injections[6-9] in addition to unscreened blood transfusion. Hepatitis C is a chronic progressive disease which causes persistent HCV viremia with elevated aminotranferase levels, histological fibrosis and cirrhosis leading to liver failure and hepatocellular carcinoma[10-11]. Recent studies have shown that combination treatment with Interferon alfa 2-b and Ribavirin for 48 weeks has given satisfactory response in these patients[12-15]. Treatment with Interferon alone for 6 months lead to early relapses[16] and US National Institute of Health consensus development conference had recommended 48 weeks treatment for better response rates and to diminish relapses[17].

Combination treatment has shown histological improvement of fibrosis in these patents[18,19] and the treatment has been found to be cost effective in these cases[20-22]. Even in cases of histologically mild chronic hepatitis C, the treatment has been found to be cost effective as compared to watchful waiting with periodic liver biopsy[23] and the treatment has also reduced the risk of hepatocellular carcinoma in these patients[24].

The aim of this study was to determine the effectiveness and safety of 48 weeks combination treatment with Interferon alfa 2b and Ribavirin in patients with chronic hepatitis C who have not been previously treated.

MATERIALS AND METHODS

The study was conducted prospectively and one hundred consecutive patients were enlisted who were found to have elevated ALT for at least 6 months. They had HCV RNA positive and a liver biopsy was performed in all patients. After the end of the treatment, no biopsies were performed as the histological improvements in treated patients have already been established in previous studies[18,19]. Quantitative HCV RNA and genotypes were not available at the time the study was started and this data is not available. Patients with compensated cirrhosis were included in the study. However, decompensated patients were excluded. Patients with pre-existing psychiatric condition,

seizure disorders, unstable Ischeamic Heart Disease and autoimmune disease were excluded. Female patients were treated after the delivery of their babies and were advised to practice effective contraception for at least 2 years.

Prior to the start of the treatment, patient had complete blood count (CBC) and were required to have haemoglobin above 12 g/dl in men and 11 g/dl in women and platelet counts were required to be above 50,000. Treatment was started with recombinant Interferon alfa 2b and Ribavirin 800–1200 mg depending on patient's weight, with patients weighing more than 75 kg receiving 1200 mg in divided doses. Interferon was given 3 million units subcutaneously three times a week. All patients were evaluated in the outpatient clinic at 2 weeks and then every 4 weeks for all 18 months. Those patients not showing a response in 12 weeks were given choice to stop the therapy, although all decided to complete the 48 weeks. They had CBC and ALT performed every month and HCV RNA was performed every 3 months and at the end of treatment at 48 weeks, and at 18 months, the end of follow up.

The Interferon alfa 2b and Ribavirin used were manufactured by Schering-Plough (Brinny), Country Cork, Ireland. Serum HCV RNA were measured by reverse transcription polymerase chain reaction assay with a sensitivity of 1000 copies per ml (Aga Khan University Hospital, Karachi). Liver biopsies were interpreted in the standard fashion with grades of inflammation ranging from 1–4 and with the stages of fibrosis from 1–4. Stages of 1–3 suggested increasing stages of fibrosis and stage 4 was interpreted as cirrhosis[25].

Efficacy of treatment was assessed with normalization of ALT and absence of serum HCV RNA measured at interval as mentioned above and being undetectable at the end of the treatment at 48 weeks which constituted end of treatment response and at the end of follow up at 18 months which constituted the sustained viral response.

Adverse effects were monitored during the each follow up visit and doses of Interferon were adjusted to two times a week or once a week if white blood cells (WBC) count dropped below 3000 and platelet counts dropped below 50000. The dosage of Ribavirin was adjusted to 1000 or 800 mg, if the haemoglobin dropped 2 g from the base line and it was held temporarily if haemoglobin dropped to 8 g and was restarted at a lower dose after an interval during which the haemoglobin recovered. The study was started in January of 1997 and all the follow-ups were completed by June 2001.

RESULTS

Out of 100 patients, 56 were males and 44 females. One male and one female discontinued treatment. Fifty-five males and 43 females, making a total of 98 patients completed the treatment. Fourteen patients had cirrhosis on liver biopsy and rest had stage 1–3 of fibrosis. Grades of inflammation varied from 1–4 in all patients. Ages of the patients ranged from 21–60 year. Most of the patients were between 31–55 years of age. The demographics of the patients treated are shown in Table-1.

Table-1: Demographic of patients treated (N=100)

Age	Male	Female	Total
18-20	0	0	0
21-25	1	0	1
26-30	4	4	8
31-35	7	7	14
36-40	7	8	15
41-45	12	8	20
46-50	13	9	22
51-55	9	6	15

56-60	3	2	5
Grand Total	56	44	100

Out of 55 males, forty-two (76.3%) had satisfactory end of treatment and thirteen were still positive for HCV RNA. Two patients relapsed giving a sustained viral response of 72.7%. Out of 43 females, 40 (93%) had end of treatment response and three patients had positive HCV RNA. Two patients relapsed giving a sustained viral response rate of 88.3%. Out of all 98 patients who completed the treatment, 82 (83.6%) had end of treatment response and 16 patients still had HCV RNA positive. A total of 4 patients relapsed with combined sustained viral response rate of 79.5% (Table-2).

Table –2: Biochemical and Virological Response (N=98)

	End of Treatment			End of Follow up			
	HCV RNA		%	HCV RNA		%	
	(-)	(+)	(-)	(-)	(+)	(-)	Total
Male	42	13	76.3	40	15	72.7	55
Female	40	3	93.0	38	5	88.3	43
Total	82	16	83.6	78	20	79.5	98

Fourteen patients who had cirrhosis on the liver biopsy, 11 were males and 3 were females. All these patients had end of treatment response but 2 relapsed giving sustained viral response rate of 85.7% in these patients (Table-3).

Table-3: Response in patients with cirrhosis (N=14)

	Number of Patients	HCV RNA (-) at End of Treatment (%)	HCV RNA (-) at End of Follow up (%)
Male	11	11 (100)	10 (90.9)
Female	3	3 (100)	2 (66.6)
Total	14	14 (100)	12 (85.7)

Ninety six percent of the patients showed normalization of ALT and negative serum HCV RNA at 24 weeks. Three patients continued to have positive HCV RNA after 6 months and, on continuing treatment, eventually became negative at the end of treatment and were still negative at the end of the follow up. One patient continued to have HCV RNA positive until 9 months and eventually became negative at the end of the treatment and remained negative at the end of follow up (Table-4).

Table-4: Timing of HCV RNA negativity in patients completing 48 weeks therapy

Time	Number of patient	Percent
3 months	94	96
6 months	3	3
9 months	1	1

The treatment was well tolerated by all patients except two patients who discontinued treatment. One was male who discontinued treatment because of un-bearable myalgias, aches and pains and one female patient discontinued because she developed psychosis. Dosage reduction was made in 15 patients due to drop in

hemoglobin below 10 g/dl and the dose was reduced in 10 patients due to drop in leukocytes counts below 2000 and platelet count below 50000. All these patients completed the treatment with adjusted dosage.

The side effects were mostly influenza-like syndrome which occurred in almost 100% patients. Gastrointestinal, psychiatric, dermatological symptoms and other side effects were tolerable and they are shown in Table-5.

Table-5: Side effects during therapy (N=98)

Adverse Effect	Number	Percent
Influenza like symptoms		
Myalgias/Arthralgias	98	100
Fever	90	92
Fatigue	70	71
Headache	68	69
Gastrointestinal		
Anorexia	56	57
Nausea/Vomiting	25	26
Abdominal pains	21	21
Psychiatric Symptoms		
Insomnia	40	41
Anxiety	30	31
Irritability/Emotional	25	26
Depression	3	3
Psychosis	2	2
Suicide	0	0
Dermatological symptoms		
Alopecia	10	10
Redness at injection site	10	10
Pruritis	8	8
Dry skin	7	7
Haematological		
Anaemia	90	92

Leucopoenia	70	71
Thrombocytopoenia	60	61
Respiratory symptoms		
Laryngitis	3	2
Others		
Bacterial Infection	2	2
Seizures	0	0

Sixteen patients who did not respond to the treatment consisted of 13 males and 3, most of them between age 50 and 60 years (mean age 48.25±7.22). Their mean ALT was 79±11, necroinflammatory score was 2.12±0.5 and fibrosis stage was 2.25±0.68.

DISCUSSION

We treated these patients for 48 weeks as previously 6 months treatment had resulted in large number of relapses and the recent recommendations from International Consensus conferences have recommended 48 weeks treatment[17,26]. Response in our patients has been excellent and this may be the effect of 48 weeks of treatment, as less relapse rate has been shown in many previous studies[13-15,18-24]. It is also likely that our patients belong to genotype Ⅲ which has good response rate[29] as this genotype has been predominantly found in Pakistan[30-31]. We had very few relapses which could have been due to our meticulous adherence to protocol.

All patient tolerated the treatment well and the side effects were in line with previously reported studies[27]. Previous psychiatric diagnosis and treatment can cause problem with these patients[28] and although we had excluded these patients from our studies, one of our patient did develop psychosis and had to discontinue treatment at 8 months of treatment and then quickly relapsed after the therapy was discontinued.

Patients with cirrhosis and chronic hepatitis C have been treated with success[32,33]. Although a European study had shown response rate of around 35%[33], our 14 patients of cirrhosis in this study, 85% had sustained viral response which is much better than previously reported in hepatitis C patients with cirrhosis. Why our patients had better results is unclear.

Previous recommendations had been that after the start of treatment, patient be checked for HCV RNA at 12 weeks and if they were still positive, the treatment should be stopped[34]. However, it has been seen that several patients will continue to have serum HCV RNA positive even at 24 weeks but will end up having good end of the treatment and end of the follow up response[26,34,35]. Four percent of our patients had delayed response and eventually had sustained viral response at the end of the follow up. Therefore, it has been suggested that '3 months stop rule' should be replaced by '6 months stop rule'[34].

Patients who do not respond to the combination treatment, continue to have lower quality of life[36]. We had 16 patients who were non-responders and such patients continue to be subject of further studies to devise effective treatments for these patients[37-39]. High dose daily injections and pegylated interferons are being tried in some patients.

In conclusion, our study shows that chronic hepatitis C patients, who have not been previously been treated, had excellent sustained viral and biochemical response with 48 weeks combination treatment with Interferon alfa 2-b and Ribavirin and the side effects have been tolerable and manageable.

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